REMARKS

Claims 1-26 and 28 currently appear in this application. The Office Action of April 13, 2007, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicant respectfully requests favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Rejections under 35 U.S.C. 112

Claims 1-14, 21, 22 and 24-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner has cited a number of phrases which are allegedly not supported in the specification.

This rejection is respectfully traversed. Support for language in the claims can be found in the specification as follows:

Claim 1, "metabolism of nitric oxide" and "perfluorocarbon." Support for "metabolism of nitric oxide" can be found in the specification at paragraph 0070, which describes how perfluorocarbons sequester circulating nitric

oxide, which can be used to treat acute hypotension and vasplegia. Administration of small amounts of perfluorocarbon (less than about 0.5% w/v) potentiates nitric oxide activity due to acceleration of NO oxidation and NO-donor formation. The specification in paragraphs 0071 through 0079 describes how administration of varying amounts of perfluorocarbons can affect a number of conditions by affecting the metabolism of nitric oxide, *i.e.*, by controlling nitric oxide bioactivity.

Support for "perfluorocarbon" can be found at paragraph 0053, as follows: "Perfluorocarbons are chemically inert, synthetic hydrophobic molecules that possess a unique capability for dissolving a variety of gases..." One commercial biomedical perfluorocarbon emulsion, Fluosol (Green Cross Corp., Osaka, Japan) is presently used as a gas carrier to oxygenate the myocardium during percutaneous coronary angioplasty.

Perfluorocarbons have also been used in diagnostic applications such as imaging.

Examples of perfluorocarbons that affect nitric oxide activity are given at paragraph 0133.

The claims have been amended to recite that the perfluorocarbons have a molecular weight of about 400 to about 700 Dalton.

Claim 2, "inhibit nitric oxide activity" is described in the specification at paragraph 0070, where it is noted that administrating about 1% w/v perfluorocarbon sequesters circulating nitric oxide. This is described in detail in paragraph 0109, describing the ability of perfluorocarbon micelles to absorb circulating NO *in vivo*.

Claims 3 and 4, the expression "enhance nitric oxide activity" finds support in the specification at paragraph 0070 as noted above, and at paragraph 0113 the action of perfluorocarbons in inhibiting nitric oxide activity and enhancing nitric oxide activity is described in detail.

Claim 5, "nucleophile" finds support in paragraph 0072, lines 5-7, "To enhance nitric oxide even further, a nucleophile is administered in conjugation with or shortly before or after administration of the perfluorocarbon."

Submitted herewith is a copy of page 205 of Morrison & Boyd, *Organic Chemistry*, Fourth Edition (1983), Allyn and Bacon, Inc., Boston, that defines "nucleophile" as electron-rich reagents that ten to attack the nucleus of carbon atoms.

In claim 6, support can be found in the specification for "thiol or mixture of thiols" at page 40, paragraph 0118, which has been amended to recite "or mixtures of thiols." This is not new matter, as claims 6, which is part of the specification as filed, recites "mixtures of

thiols." Additional support for thiols can be found at page 52, paragraph 0136, which lists several thiols that are particularly well suited to be used as nucleophiles in the process claimed herein.

Claim 8 recites a number of conditions that can be treated by the method claimed herein. Support or these treatments is found in the specification at pages 22 and 23, paragraph 0068 and pages 28-30, paragraphs 0094-0104.

"Nitrosative stress" in claim 21 finds support in the specification as filed at page 32, paragraph 0108, "These results suggest that by using various amounts of perfluorocarbon together with low molecular weight nucleophiles, one can regulate the level of endogenous vasoactive low molecular weight S-nitrosothiols. Notably, uncoupling NO-donors formation from overall NO synthesis not only provides a new way to control blood pressure and organ perfusion, but also creates a unique opportunity to relieve nitrosative stress (excessive nitration and nitrosation of proteins and nucleic acids) during inflammation (Poli, 2002; Beckman et al., 1996; Beckman et al., 1994)."

For claim 22, support for "regulating perturbations" can be found in the specification at pages 25 and 26, paragraph 0079, "Administering perfluorocarbons to regulate nitric oxide activity can also be used to treat osteoporosis,

Paget bone disease, and rheumatoid arthritis by regulating perturbations in the interactions between local and systemic bone-remodeling regulatory pathways."

Claim 27 has been cancelled.

The Examiner alleges that the specification is devoid of disclosure that would direct the skilled artisan to all disorders or conditions embraced by the claims. The Examiner has suggested specific disorders or conditions be disclosed, as such would appear to obviate the rejection. However, it is respectfully submitted that specific disorders and conditions have been disclosed, most notably at pages 24-26.

It is known that regulating nitric oxide activity can be used to treat a great variety of disorder and conditions. However, previously the only compounds used to generate nitric oxide *in vivo* clinically are nitroglycerin, amyl nitrite and sodium nitroprusside. These compounds, as described on pages 7 and 8 of the specification, have a short duration of action, a short half-life, a lack of tissue specificity, development of tolerance, and accumulation of toxic substances (sodium cyanide in the case of sodium nitroprusside).

Use of nitric oxide to treat many conditions and disorders is described in the specification as filed at page 1, paragraph 0003 through page 20, paragraph 0052. S-nitrosothiols are potent vasodilators and antiplatelet agents. The presently claimed method provides a synthetic hydrophobic phase, perfluorocarbons, for catalyzing nitric oxide oxidation and formation of nitrosothiols.

An experiment described beginning at paragraph 0108 on page 31 shows the stimulating effect of perfluorocarbons on the formation of S-nitrosothiols. Figure 4A and the example beginning at page 33, paragraph 0109, illustrates that perfluorocarbons are powerful NO sink *in vivo* and catalyst of S-nitrosothiols.

The specification beginning on page 8, at paragraph 0020, discusses the effect of S-nitrosothiols *in vivo*. Paragraph 0022 notes that there are data to suggest that S-nitrosothiols have a possible place in the management of a variety of diseases. Paragraph 0025-0048 discusses specific uses of RSNOs as therapeutic agents; the herein claimed methods generate such useful compounds *in vivo* and can maintain the activity level of the compounds over a period of time. S-nitrosothiols have been considered to be promising therapeutics for a variety of acute and chronic conditions,

and the presently claimed methods provide improved methods for generating these compounds *in vivo*.

With respect to amounts to be administered, the specification provides clear guidance at page 53, paragraph 0141, "For inhibiting nitric oxide activity, the perfluorocarbon should be administered in amounts of at least about 0.5% w/volume of blood or more. The perfluorocarbon can be administered in larger quantities, *.e.g.*, up to about 10% w/volume of blood, depending upon the condition of the patient and the particular problem to be treated. For enhancing the effects of nitric oxide, the perfluorocarbons should be administered in amounts of less than about 0.5% w/volume of blood, and generally in amounts ranging from about 0.01% to about 0.1% w/volume of blood. These amounts will vary with the individual and the condition to be treated."

Since one skilled in the art can readily determine whether a condition to be treated requires inhibition of nitric oxide activity or enhancement of nitric oxide activity, the skilled artisan can readily, without undue experimentation, determine the amount of perfluorocarbon to be administered.

Claims 1-14, 21, 22 and 24-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is respectfully traversed. The word "perfluorocarbon" is not of indefinite scope, as the specification describes perfluorocarbons at paragraph 0053 on page 20 as being chemically inert synthetic hydrophobic molecules that possess a unique capability of dissolving a variety of gases, including O_2, CO_2 and NO. The claims have been amended to recite that the molecular weight soft the perfluorocarbons should lie within the limits of about 400-700 Daltons. Claim 28 has been added to recite that the optimal particle size of the perfluorocarbon micelles is from about 25 m, to about 1 microns, as stated at paragraph 0131, page 49.

The plethora of intended uses present in the claims does not render the intended "amount" ambiguous. One skilled in the art can readily determine if a patient needs to have the action of nitric oxide inhibited or enhanced. The activity of nitric oxide can be inhibited by administering more than about 0.5% w/volume of blood of the perfluorocarbon, and the activity of nitric oxide can be enhanced by administering more than about 0.5% w/volume of blood of the

perfluorocarbon, as detailed in the experiments, beginning at page 33, paragraph 0109.

In rejecting the claims on art, the Examiner has cited Garfield, U.S. Patent No. 5,869,539. This patent is directed to administering nitric oxide directly to patients in need thereof. Garfield, which issued in 1999, describes many conditions that can be treated by administering nitric oxide. Beginning at column 2, line 34, Garfield notes that there is a substantial body of evidence from animal studies that a deficiency in nitric oxide contributes to the pathogenesis of a number of diseases. That is, as of 1989, it was known that many conditions can be treated by administering nitric oxide. The presently claimed method, rather than administering nitric oxide, administers a fluorocarbon, which enhances nitric activity in the patient or inhibits nitric oxide activity in a patient, depending on the amount administered. Therefore, it is respectfully submitted that one skilled in the art could readily determine whether to enhance or inhibit nitric oxide activity to treat a specific condition, as the connection between nitric oxide activity and a great variety of conditions and diseases is well known.

Art Rejections

Claims 1, 8-14 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Garfield et al., U.S. 5,869,539.

This rejection is respectfully traversed. Garfield discloses treating a variety of conditions by administering an emulsion of perfluorocarbon in which nitric oxide is dissolved. That is, Garfield treats these conditions by administering nitric oxide, using the perfluorocarbon as a **carrier** for the nitric oxide. The presently claimed method differs from this in that nitric oxide is not administered, but the perfluorocarbon is administered to generate S-nitrosothiols *in vivo*. In fact, in the case in which the activity of nitric oxide is inhibited, administering nitric oxide would be contraindicated.

Claims 1-4, 8-14, 21, 22, 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garfield et al.

This rejection is respectfully traversed. Garfield discloses administering nitric oxide dissolved in a perfluorocarbon. The presently claimed method, hosed, is directed to administering a perfluorocarbon to inhibit or to enhance nitric oxide activity. No nitric oxide is administered.

As noted above, the perfluorocarbon is administered in amounts of less than about 0.5% w/volume in order to enhance nitric oxide activity, while the perfluorocarbon is administered in amounts of more than about 0.5% w/volume in order to inhibit nitric oxide activity. There is nothing in Garfield regarding inhibiting nitric oxide activity, nor would one skilled in the art reading Garfield administer only perfluorocarbon in order to enhance nitric oxide activity. Where Garfield administers nitric oxide dissolved in a perfluorocarbon, the herein claimed method administers a perfluorocarbon to affect endogenous nitric oxide activity.

With regard to the amounts administered, the present inventors have discovered that the amount of perfluorocarbon administered directly affects the nitric oxide activity by either enhancing or inhibiting nitric oxide activity. There is nothing in Garfield about affecting nitric oxide activity, as Garfield administers nitric oxide. Moreover, there is nothing that would lead one skilled in the art to increase the amount of perfluorocarbon administered in order to inhibit nitric oxide activity.

There is nothing in Garfield regarding inhibiting nitric oxide activity, as administering nitric oxide dissolved in a perfluorocarbon would certainly not be done to inhibit nitric oxide activity.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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In an alkyl halide, halogen is attached to carbon; and, just as halide readily releases a proton, so it readily releases carbon—again, to other bases. These bases possess an unshared pair of electrons and are seeking a relatively positive site, that is, are seeking a nucleus with which to share their electron pair.

Basic, electron-rich reagents that tend to attack the nucleus of carbon are called **nucleophilic reagents** (from the Greek, *nucleus-loving*) or simply **nucleophiles**. When this attack results in substitution, the reaction is called **nucleophilic substitution**.

$$\underset{\text{Substrate}}{R{:}X} + \underset{\text{Nucleophile}}{{:}Z} \longrightarrow R{:}Z + \underset{\substack{\text{Leaving}\\ \text{group}}}{{:}X^-}$$

The carbon compound that undergoes a particular kind of reaction—here, the compound on which substitution takes place—is called the **substrate**. In the case of nucleophilic substitution, the substrate is characterized by the presence of a **leaving group**: the group that becomes displaced from carbon and, taking the electron pair with it, departs from the molecule.

Increasingly in the chemical literature, we find the leaving group called the *nucleofuge* (from the Latin, *nucleus-leaver*). It is said to be *nucleofugic*, and it possesses *nucleofugality*.

In the example we started with, methyl bromide is the substrate, bromide is the leaving group, and hydroxide ion is the nucleophile.

Because the weakly basic halide ion is a good leaving group, then, alkyl halides are good substrates for nucleophilic substitution. They react with a large number of nucleophilic reagents, both inorganic and organic, to yield a wide variety of important products. As we shall see, these reagents include not only negative ions like hydroxide, alkoxide, and cyanide, but also neutral bases like ammonia and water; their characteristic feature is an unshared pair of electrons.

As a synthetic tool, nucleophilic substitution is one of the three or four most useful classes of organic reactions. Nucleophilic substitution is the work-horse of organic synthesis; in its various forms, it is the reaction we shall turn to first when faced with the basic job of replacing one functional group by another. The synthesis of aliphatic compounds, we said, most often starts with alcohols. But the —OH group, we shall find, is a very poor leaving group; it is only conversion of alcohols into alkyl halides—or other compounds with good leaving groups—that opens the door to nucleophilic substitution.

A large number of nucleophilic substitutions are listed below to give an idea of the versatility of alkyl halides; many will be left to later chapters for detailed discussion.

With nucleophilic substitution we shall encounter many things new to us: a new reaction, of course—several new reactions, actually—and a new kind of reactive particle, the *carbocation*. To find out what is going on in these reactions, we shall use a new tool, *kinetics*, and use an old tool, *stereochemistry*, in a new way. We shall be introduced to new factors affecting reactivity—*dispersal of charge* and *polar factors*, *steric hindrance*, *nucleophilic assistance*—factors that we shall work with throughout the rest of our study.

We shall see how reactivity—and, with it, the course of reaction—is affected by the *solvent*. The solvent adds a new dimension to our study of organic chemistry; if it complicates things, it at the same time adds richness. It offers us the most